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How to Use Cerebral Vasodilators and Metabolic Activators

Kazuo ISOZUMI and Yoshio IZUMI*

Department of Neurology, Ashikaga Red Cross Hospital
**Department of Neurology, Tokai University School of Medicine*

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Cerebral vasodilators and metabolic activators (enhancers) for the treatment of cerebrovascular disorders (CVD) have been categorized and introduced into clinical practice according to their pharmacological actions and clinical indications. The main therapeutic goal of these drugs is to relieve residual subjective symptoms and neuropsychological dysfunction, which reduce the quality of life of patients in the chronic stage of stroke. Selection of the most suitable drug for the individual symptoms of each patient is an important therapeutic principle.

Key words : cerebral vasodilators, cerebral metabolic activators, cerebral metabolic enhancers, cerebral blood flow, cerebral metabolism, cerebrovascular disorders, stroke

INTRODUCTION

Cerebral vasodilators and metabolic activators (enhancers) have a history of over 30 years since they started to be used in the routine clinical setting, and over 30 drugs in this category are now available. These drugs are divided into two major groups: one is "cerebral vasodilators" which dilate cerebral vessels and increase cerebral blood flow (CBF), and the other is "cerebral metabolic activators" which enhance cerebral metabolism [6]. These drugs are mainly used for the chronic stage of stroke, and their effectiveness is assessed from improvement of residual subjective symptoms and neuropsychological dysfunction [10, 30].

Assessment of the effectiveness of cerebral vasodilators and metabolic activators has been carried out in randomized, placebo-controlled trials. Major observations include (1) subjective symptoms, (2) psychological symptoms, (3) neurological symptoms (dysphagia, dysarthria/dysphasia, motor dysfunctions, etc.) and (4) ADL (activities of daily living: sitting, walking, dining, washing the face, going to the lavatory, taking a bath, etc.). Effectiveness has been assessed according to these items on the basis of changes in the severity of symptoms before and after use of the drugs [30].

Common psychological sequelae of stroke are depression, hypobulia, disorientation, night delirium, hallucinations, and delusions. Cerebral metabolic activators are effective against these psychological symptoms in approximately 60% of patients. They are also effective against subjective symptoms such as headache, dull headache, dizziness, numbness of the limbs, and fatigability. Cerebral vasodilators generally show superior improvement of subjective symptoms. Improvement of intellectual disturbances such as memory defect and dyscalculia, neurological symptoms such as motor paresis, and ADL can be achieved with cerebral metabolic activators regrettably in only 30% of patients [30].

In this brief review, cerebral vasodilators and metabolic activators are categorized and introduced for practical use according to their pharmacological actions and clinical indications [24].

Cerebral metabolic activators (Table 1)

Cerebral metabolic activators have recently been classified into modulating, enhancing and suppressive drugs according to their clinical efficacy. Enhancing drugs are used in patients who mainly show negative symptoms such as a depressive mood, hypobulia or a reduction in spontaneity. Suppressive drugs are used for patients who mainly show positive symptoms such as anxiety, fretfulness, restlessness, excitement and night delirium. Modulating drugs are used

Kazuo ISOZUMI, Department of Neurology, Ashikaga Red Cross Hospital, 3 - 2100 Honjo, Ashikaga, Tochigi 326 - 0808 Japan

Table 1 Classification of cerebral metabolic activators according to clinical indications

1) Cases showing negative symptoms (depressive mood, hypobulia or reduced spontaneity)	
Bifemelane hydrochloride	50 mg, p. o., 3 times a day
Lisuride maleate [5]	0.025 mg, p. o., 3 times a day
Amantadine hydrochloride	50 mg, p. o., 2-3 times a day
2) Cases showing positive symptoms (anxiety, fretfulness, restlessness, excitement and night delirium)	
Aniracetam	200 mg, p. o., 3 times a day
Tiapride hydrochloride	25 mg, p. o., 1-3 times a day
3) Cases showing both negative and positive symptoms	
Indeloxazine hydrochloride	20 mg, p. o., 3 times a day
Propentofylline	100 mg, p. o., 3 times a day
Idebenone [38]	30 mg, p. o., 3 times a day

Table 2 Classification of cerebral vasodilators according to clinical indications

1) Cases associated with hypertension	
Nicardipine hydrochloride	20 mg, p. o., 3 times a day
Nilvadipine	2 mg, p. o., twice a day
2) Cases associated with equilibrium disorders (vertigo, dizziness)	
Ifenprodil tartrate	20 mg, p. o., 3 times a day
Difenidol hydrochloride	25-50 mg, p. o., 3 times a day
Betahistine mesilate	6-12 mg, p. o., 3 times a day
3) Cases associated with ischemic heart disease	
Dilazep dihydrochloride	50-100 mg, p. o., 3 times a day
Trapidil	100 mg, p. o., 3 times a day
4) Cases requiring hematological improvemenets	
Pentoxifylline	100 mg, p. o., 3 times a day
Cinnarizine [3]	25-50 mg, p. o., 3 times a day
Flunarizine hydrochloride [37]	10 mg, p. o., once a day
5) Cases requiring improvement in cerebral metabolism	
Brovincamine fumarate	20 mg, p. o., 3 times a day
Vinpocetine	5 mg, p. o., 3 times a day
Moxisylyte hydrochloride	30 mg, p. o., 3 times a day
Nicergoline	5 mg, p. o., 3 times a day
6) Cases requiring prevention of recurrence of cerebral infarction	
Dilazep dihydrochloride	50-100 mg, p. o., 3 times a day
Ifenprodil tartrate	20 mg, p. o., 3 times a day
Ibudilast	10 mg, p. o., 3 times a day

for patients who show both negative and positive symptoms.

1) Drugs for negatives symptoms

Bifemelane hydrochloride [19] and **indeloxazine hydrochloride** [33] are substances discovered during the development of antidepressants. Unlike conventional antidepressants, they do not possess a central anticholinergic effect and are effective against negative symptoms such as hypobulia or depression. **Propentofylline** [22] is an adenosine uptake blocker which enhances cerebral glucose matabolism. It significantly improves psychiatric symptoms such as expression deficiency, hypobulia, anxiety, fretfulness, and depression [28]. **Amantadine hydrochloride** [36] has been primarily used as antiparkinsonian drug because of its stimulative effect on dopamine neurons. It is also a cerebral metabolic activator, and its clinical efficacy becomes apparent within two weeks, a comparatively short period for cerebral metabolic activators. Therefore, it is useful for rehabilitation in patients with hypobulia or reduced spontaneity.

2) Drugs for positive symptoms

Aniracetam [31] is a newly developed cognition-enhancing agent which exerts a stimulatory effect on specific central cholinergic pathways. This drug features specific efficacy against night delirium, wandering and urinary incontinence when compared with conventional cerebral metabolic activators. Coventional cerebral metabolic activators are generally effective against negative symptoms, and have little effect on positive symptoms such as excitement, aggressive behavior, delirium and wandering. Antipsychotic agents such as haloperidol or chlorpromazine hydrochloride are commonly used for such symptoms. **Tiapride hydrochloride** [1] possesses a dopamine receptor antagonistic effect, and was originally used for dyskinesia in L-DOPA treated parkinsonism. It is also effective against positive symptoms, and is used as a substitute for or for reduction of the dosage of antipsychotics.

Cerebral vasodilators (Table 2)

The main actions of cerebral vasodilators are dilatation of cerebral vessels and increase of CBF. When cerebral vasodilators are used to treat stroke sequelae, they are most effective against subjective symptoms such as headache, dull headache, and dizziness in about 70% of patients. They are also effective against psychiatric symptoms such as hypobulia or depression in 30 to 40% of patients. However, they are not so effective against neurological symptoms and hardly improve ADL. Since cerebral vasodilators usually have several pharmacological actions, they should be selected according to individual patient's conditions.

1) Cases associated with hypertension

In cases associated with hypertension, excessive reduction of blood pressure may induce reinfarction. On the other hand, persistent hypertension is also a risk factor of reinfarction [13]. **Nicardipine hydrochloride** [26] and **nilvadipine** [7] are calcium channel blocking cerebral vasodilators with hypotensive action. They were originally developed as calcium channel blocking antihypertensives, and are the only two agents in this category which have been recognized to be effective as cerebral vasodilators. Since they have strong cerebrovascular selectivity, they do not reduce CBF, but actually increase CBF and simultaneously decrease systemic blood pressure.

2) Cases associated with equilibrium disorders such as vertigo or dizziness

Ifenprodil tartrate [2] selectively increases vertebrobasilar blood flow, especially on the affected side and corrects imbalance between the affected and unaffected sides. This drug improves symptoms of patients with vertebrobasilar insufficiency. **Difenidol hydrochloride** [21] is an agent to imporve dysequilibrium which increases vertebrobasilar blood flow especially on the affected side, adjusts the function of vestibular neuronal tracts, suppresses nystagmus, and is effective against vertigo. **Betahistine mesilate** [27] increases blood flow of the internal ear and improves endolymphatic hydrops. It also increases blood flow of the internal carotid artery. This agent is prescribed as for vertigo and other equilibrium disorders and is also used to treat Meniere's disease.

3) Cases associated with ischemic heart disease

Dilazep dihydrochloride [20] possesses coronary vasodilating effects and is applied as an analgesic in ischemic heart disease and

angina pectoris. It rapidly relieves angina attacks and can reduce dosage of nitrates. It also improves subjective symptoms such as palpitation and dyspnea, and increases cerebral and renal blood flow. **Trapidil** [4] has coronary dilating and anti-PDGF (platelet-derived growth factor) effects. It improves cardiac function in patients with angina pectoris. It reduces the frequency of angina attacks and improves exercise capacity. It also possesses platelet aggregation inhibitory and lipid metabolism improving effects.

4) Cases requiring hematological improvements

Pentoxifylline [34] increases red blood cell deformability and decreases fibrinogen. Since it decreases blood viscosity and improves oxygen dissociation, it improves microcirculation and increases oxygen supply to the brain tissue. Pentoxifylline also normalizes excessive red blood cell aggregation.

5) Cases requiring improvements in cerebral metabolism

Cerebral metabolic activators are usually superior to cerebral vasodilators in the improvement of psychiatric symptoms, while cerebral vasodilators are better than cerebral metabolic activators in the improvement of subjective symptoms. Agents possessing both properties are effective against psychiatric symptoms such as hypobulia and emotional disturbance in addition to improvement of subjective symptoms. **Brovincamine fumarate** [35] is a vincamine derivative, which has delayed cerebrovascular dilatation effects as a calcium blocker [18]. It also accelerates biosynthesis of noradrenaline and serotonin. **Vinpocetine** [23] increases cyclic GMP, dilates vascular smooth muscle and selectively increases CBF with activation of cerebral metabolism as an additional function. **Moxisylyte hydrochloride** [32] is an α_1-receptor blocker which selectively dilates cerebral vessels. When it is administered over a long period, systemic blood pressure is slightly decreased and CBF is increased together with improvement of cerebral metabolism and protection of ischemic brain tissue. **Nicergoline** [39], an ergot derivative [8], selectively blocks α_1-receptors and increases CBF [11, 12, 14]. It also enhances cholinergic and dopaminergic neurotransmission [16, 17].

6) Cases requiring prevention of recurrence of cerebral infarction

Dilazep dihydrochloride [20] inhibits phospholipase, normalizes platelet function and prevents recurrence of transient ischemic attacks (TIA) and cerebral infarction. **Ifenprodil tartrate** [2] has a platelet membrane stabilizing effect and also prevents recurrence of TIA and cerebral infarction. Since **ibudilast** [25] antagonizes leukotriene and platelet activating factor (PAF), and enhances prostacyclin (PGI_2) [15], it is used as an antiallergic agent to treat bronchial asthma [29] in addition to the prevention of TIA and cerebral infarction. These cerebral vasodilators with preventive effects on TIA and cerebral infarction do not pose any significant risk of cerebral hemorrhage or gastro-intestinal bleeding. Therefore, they can be used in elderly patients or those whose previous stroke was not clearly distinguished as a cerebral hemorrhage or infarction [9].

CONCLUDING REMARKS

Typical cerebral metabolic activators and vasodilators have been introduced and outlined. The objective of these agents is to reduce subjective symptoms such as headache and dizziness, and psychiatric symptoms such as hypobulia and depression as sequelae of stroke. This promotes effective rehabilitation and smooth adaptation to society. On the other hand, it should be understood that these products can not sufficiently improve intellectual function or neurological symptoms such as hemiplegia. Therefore, they have pharmacological limitations.

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